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(71) Applicant (for all designated States except AT, US): NOVARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

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(71) Applicant (for AT only): NOVARTIS-ERFINDUNGEN

VERWALTUNGSGESELLSCHAFT M.B.H. [AT/AT];  
Brunner Strasse 59, A-1230 Vienna (AT).

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(72) Inventor; and

(75) Inventor/Applicant (for US only): STEELE, Ronald,  
Edward [US/US]; 101 Naughtright Road, Long Valley,  
NJ 07853 (US).

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(54) Title: COMBINATION OF ORGANIC COMPOUNDS

(57) Abstract: The invention relates to a pharmaceutical composition, of (i) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof either alone or in combination with (ii) an AT<sub>1</sub>-receptor antagonist combined with a diuretic, or in each case, a pharmaceutically acceptable salt thereof and (iii) a pharmaceutically acceptable carrier.

Combination of Organic Compounds

The invention relates to a pharmaceutical composition comprising

- (i) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof alone or in combination with,
- (ii) an AT<sub>1</sub>-receptor antagonist or an AT<sub>2</sub> receptor antagonist combined with a diuretic or, in each case, a pharmaceutically acceptable salt thereof and
- (iii) a pharmaceutically acceptable carrier.

The invention furthermore relates to a method for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of

- (a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
- (b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension; and
- (c) endothelial dysfunction with or without hypertension, comprising administering the pharmaceutical composition of the present invention.

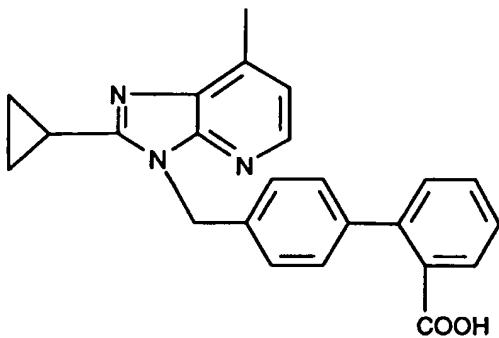
In a preferred embodiment the present invention relates to a method of prevention of, delay of progression of or treatment of endothelial dysfunction with or without hypertension comprising administering to a warm-blooded animal, including man, in need thereof an effective amount of an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof.

AT<sub>1</sub>-receptor antagonists (also called angiotensin II receptor antagonists) are understood to be those active ingredients which bind to the AT<sub>1</sub>-receptor subtype of angiotensin II receptor but do not result in activation of the receptor. As a consequence of the inhibition of the AT<sub>1</sub>

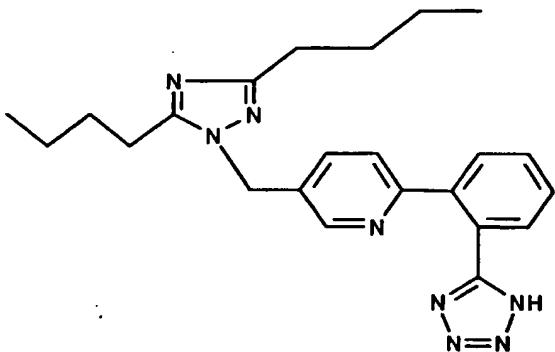
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receptor, these antagonists can, for example, be employed as antihypertensives or for treating congestive heart failure.

The class of AT<sub>1</sub> receptor antagonists comprises compounds having differing structural features, essentially preferred are the non-peptidic ones. For example, mention may be made of the compounds which are selected from the group consisting of valsartan, losartan, candesartan, eprosartan, irbesartan, saprisartan, tasosartan, telmisartan, the compound with the designation E-1477 of the following formula

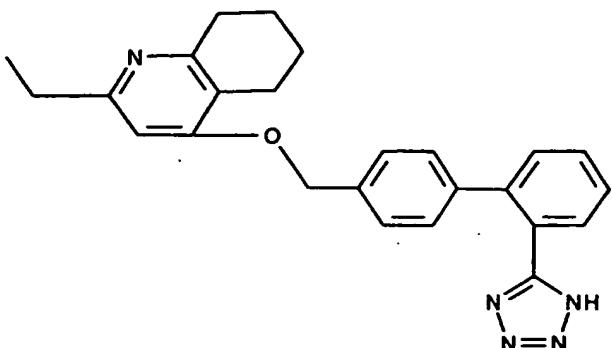


the compound with the designation SC-52458 of the following formula



and the compound with the designation the compound ZD-8731 of the following formula

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or, in each case, a pharmaceutically acceptable salt thereof.

Preferred AT<sub>1</sub>-receptor antagonist are those agents which have been marketed, most preferred is valsartan or a pharmaceutically acceptable salt thereof.

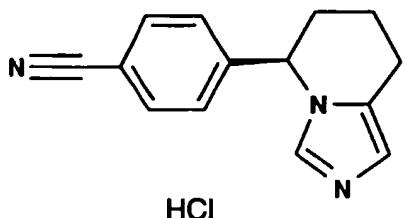
A diuretic is, for example, a thiazide derivative selected from the group consisting of chlorothiazide, hydrochlorothiazide, methylclothiazide, and chlorothalidone. The most preferred is hydrochlorothiazide.

Aldosterone synthase inhibitor is an enzyme which converts corticosterone to aldosterone by hydroxylating corticosterone to form 18-OH-corticosterone and 18-OH-corticosterone to aldosterone. The class of aldosterone synthase inhibitors known to be applied for the treatment of hypertension and primary aldosteronism comprises both steroid and non-steroid aldosterone synthase inhibitors, the latter being most preferred.

Preference is given to commercially available aldosterone synthase inhibitors or those aldosterone synthase inhibitors that have been approved by the health authorities.

The class of aldosterone synthase inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds which are selected from the group consisting of the non-steroidal aromatase inhibitors anastrozole, fadrozole (including the (+)-enantiomer thereof), as well as the steroid aromatase inhibitor exemestane, or, in each case where applicable, a pharmaceutically acceptable salt thereof.

The most preferred non-steroidal aldosterone synthase inhibitor is the (+)-enantiomer of the hydrochloride of fadrozole (US patents 4617307 and 4889861) of formula



Surprisingly, the pharmaceutical compositions according the present invention exhibit a beneficial, especially a synergistic (= more than additive), therapeutic effect, furthermore benefits resulting from combined treatment such as a surprising prolongation of efficacy, a broader variety of therapeutic treatment and surprising beneficial effects on diseases and conditions associated with AT<sub>1</sub>-receptors or aldosterone synthase inhibitors, respectively.

The compositions according to the present invention can be used for the prevention of, the delay of progression of and treatment of a disease or condition selected from the group consisting of

- (a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
- (b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension; and
- (c) endothelial dysfunction with or without hypertension.

The person skilled in the pertinent art is fully enabled to select a relevant animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects.

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These beneficial effects can, for example, be demonstrated in the test model as disclosed by G. Jeremic et al. in J. Cardovasc. Pharmacol. 27:347-354, 1996.

#### **Study design**

In the study to be performed, permanent coronary artery occlusion (CAO) in rats is used as a model of acute myocardial infarction. The experiments are carried out with 5 treatment groups characterized by following features:

- sham-operated animals
- CAO + vehicle
- CAO + valsartan
- CAO + aldosterone synthase inhibitor
- CAO + AT<sub>1</sub>-receptor antagonist + aldosterone synthase inhibitor.

Following doses and routes of administration can be applied:

For example for the AT<sub>1</sub>-receptor antagonist valsartan

- a) -3d to +2d: s.c. injections 2.5 mg/kg BW/12 h
- b) +3d to +28d: s.c. Alza osmotic minipumps 5 mg/kg/d

For the (+)-enantiomer of the hydrochloride of fadrozole

Alza osmotic minipumps 0.4 mg/kg/d.

During the study following variables are measured:

- infarct size
- LV chamber volume
- interstitial and perivascular collagen density in spared LV myocardium
- COL-I and COL-III protein content in spared LV myocardium by Western blot
- cardiomyocytes cross-sectional area and length in sections of LV myocardium
- plasma concentrations of Ang II and aldosterone
- urine concentration of sodium, potassium and aldosterone
- blood pressure in conscious animals
- LV and carotid blood pressure in anesthetized animals.

#### **Methodology**

**Infarct size:** Six µm-thick transverse histological sections of the left ventricle are stained with nitroblue tetrazolium and acquired by a B/W XC-77CE CCD video camera (Sony). The resulting image is processed on a KS 300 image analysis system (Carl Zeiss Vision) using a

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software specifically developed (Porzio *et al.*, 1995). A single operator blinded to treatment interactively defines the boundaries of the interventricular septum, and the infarcted area on each section is semiautomatically identified as the area of unstained ventricular tissue. The software automatically calculates for each component of the ventricular section defined as the chamber, septum, infarcted area, infarcted LV wall and viable LV wall, a set of geometric parameters (Porzio *et al.*, 1995).

**Histology:** Hearts are fixed *in situ*, by retrograde perfusion with buffered 4% formaldehyde after arrest in diastole by i.v. injection of 0.5 M KCl. After fixation, the left ventricle (LV) and the free wall of the right ventricle are separately weighed; LV longer diameter is measured with a caliper. LV histological sections are stained with hematoxylin & eosin for qualitative examination and to quantify cardiomyocytes cross-sectional area with a semi-automated image analysis routine. Interstitial collagen deposition in LV is evaluated on Sirius red stained sections with a semi-automated image analysis routine (Masson *et al.*, 1998).

**Collagen content in LV spared myocardium:** LV tissue in the spared myocardium is homogenized, subjected to PAGE-SDS electrophoresis and electroblotted onto nitrocellulose membrane. The blots are exposed to primary antibodies, i.e. rabbit anti-rat collagen type I or type III antiserum (Chemicon). The primary antibodies are recognized by secondary antibodies conjugated to alkaline phosphatase (for collagen type I) or peroxidase (collagen type III).

**Left ventricular chamber volume:** LV chamber volume is determined in hearts arrested in diastole (KCl) and fixed in formalin under a hydrostatic pressure equivalent to the measured LV end-diastolic pressure. A metric rod is inserted into the LV to measure LV inner length. The transverse diameters of the LV chamber are measured in two 1-mm thick transverse sections near to the base and the apex of the ventricle (Jeremic *et al.*, 1996). The chamber volume is computed from an equation integrating transverse diameters and inner length.

**Systemic and Left ventricular hemodynamics:** A microtip pressure transducer (Millar SPC-320) connected to a recorder (Windograf, Gould Electronics) is inserted into the right carotid artery to record systolic and diastolic blood pressures. The pressure transducer is advanced into the LV to measure LV systolic (LVSP) and end-diastolic (LVEDP) pressures, the first derivative of LV pressure over time ( $+dP/dt$ ) and heart rate.

**Non-invasive blood pressure:** Systolic blood pressure and heart rate are measured by the tail-cuff method (Letica LE 5002) in conscious rats.

**Urine electrolytes, hormones:** Rats are individually housed in metabolic cages and 24-h urine collected on 1 ml HCl 6N. Water intake is measured. Urine catecholamines are extracted on Bondelut C<sub>18</sub> columns (Varian), separated by HPLC (Apex-II C<sub>18</sub>, 3 µm, 50x4.5 mm analytical column, Jones Chromatography) and quantified with an electrochemical detector (Coulochem II, ESA) (Goldstein *et al.*, 1981). Plasma and urine aldosterone, and plasma angiotensin II is determined with specific radioimmunoassays (Aldoctx-2, DiaSorin and Angiotensin II, Nichols Diagnostics). Urine sodium and potassium are measured by flamme photometry.

**Sample size**

10 animals analyzable in each treatment groups are sufficient to detect biologically significant differences. Only rats with an infarct size of at least 10% of the LV section area are included in the final analysis.

Accordingly, the composition of the present invention can be used for the prevention of, delay of progression of, and treatment of survival post myocardial infarction (MI).

**Endothelial dysfunction** is being acknowledged as a critical factor in vascular diseases. The endothelium plays a bimodal role as the source of various hormones or by-products with opposing effects: vasodilation and vasoconstriction, inhibition or promotion of growth, fibrinolysis or thrombogenesis, production of anti-oxidants or oxidising agents. Genetically predisposed hypertensive animals with endothelial dysfunction constitute a valid model for assessing the efficacy of a cardiovascular therapy.

Endothelial dysfunction is characterized by, for example, increased oxidative stress, causing decreased nitric oxide, increased factors involved in coagulation or fibrinolysis such as plasminogen activating inhibitor-1 (PAI-1), tissue factor (TF), tissue plasminogen activator (tPA), increased adhesion molecules such as ICAM and VCAM, increased growth factors such as bFGF, TGF $\beta$ , PDGF, VEGF, all factors causing cell growth, inflammation and fibrosis.

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The treatment e.g. of endothelial dysfunction can be demonstrated in the following pharmacological test:

**Material and methods**

Male 20-24 week-old SHR, purchased from RCC Ltd (Fullingsdorf, Switzerland), are maintained in a temperature- and light-controlled room with free access to rat chow (Nafag 9331, Gossau, Switzerland) and tap water. The experiment is performed in accordance with the NIH guidelines and approved by the Canton Veterinary office (Bew 161, Kantonales Veterinäramt, Liestal, Switzerland). All rats are treated with the NO synthase inhibitor L-NAME (Sigma Chemicals) administered in drinking water (50 mg/l) for 12 weeks. The average daily dose of L-NAME calculated from the water consumed was 2.5 mg/kg/d (range 2.1-2.7 ).

The rats are divided into 5 groups: group 1, control (n = 40); Group 2, valsartan (5 mg/kg/d; n = 40); Group 3, the (+)-enantiomer of the hydrochloride of fadrozole (n = 30); Group 4, a combination of the (+)-enantiomer of the hydrochloride of fadrozole and valsartan (5 mg/kg/d; n = 30) and Group 5, valsartan (50 mg/kg/d; n = 30). The drugs are administered in drinking fluid. The pressor effect of Ang II at 1 mg/kg obtained in controls normotensive rats is reduced by 49 % and 73 % after treatment with valsartan 5 and 50 mg/kg/d , respectively (Gervais et al. 1999). The response to Ang I injected in Wistar Kyoto rats pretreated with the (+)-enantiomer of the hydrochloride of fadrozole or valsartan 5 mg/kg/d is similar.

Body weight is measured every week. Systolic blood pressure and heart rate are recorded by tail cuff plethysmography 3 and 2 weeks before starting the study and at 2 weeks after drug administration. Urine is collected over a 24 hour period from rats kept in individual (metabolic) cages the week before starting treatment and at weeks 4 and 12 for volume measurement and protein, creatinine, sodium and potassium determination using standard laboratory methods. At the same time points, blood samples are withdrawn from the retro-orbital plexus (maximum 1 ml) for creatinine, Na<sup>+</sup> and K<sup>+</sup> assays.

Ten rats from each group are sacrificed at 4 weeks for collection of kidney and heart for morphological analysis. The remaining rats are sacrificed at 12 weeks. Cardiac and kidney

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weight is recorded. Terminal blood sampling is performed in 5 % EDTA at 4 (morphometry study) and 12 (end of the study) weeks for aldosterone, determination by radioimmunoassay using a DPC coat-a-count aldosterone-RIA kit (Bühlmann, Switzerland).

**Statistical analysis:**

All data are expressed as mean  $\pm$  SEM. Statistical analysis is performed using a one-way ANOVA, followed by a Duncan's multiple range test and a Newman-Keuls test, for comparison between the different groups. Results with a probability value of less than 0.05 are deemed statistically significant.

An improvement of regression of atherosclerosis without effecting the serum lipid levels can, for example, be demonstrated by using the animal model as disclosed by H. Kano et al. in Biochemical and Biophysical Research Communications 259, 414-419 (1999).

That the compounds or combinations according to the present invention can be used for the regression of a cholesterol diet-induced atherosclerosis, can be demonstrated using the test model described, e.g., by C. Jiang et al. in Br. J. Pharmacol. (1991), 104, 1033-1037.

That the compounds or compositions according to the present invention can be used for the treatment of renal failure, especially chronic renal failure, can be demonstrated using the test model described, e.g., by D. Cohen et al. in Journal of Cardiovascular Pharmacology, 32: 87-95 (1998).

Further benefits when applying the composition of the present invention are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side effects. This is in accordance with the desires and requirements of the patients to be treated.

All the more surprising is the experimental finding that the combined administration of combination according to the present invention results in a beneficial, especially a synergistic, therapeutic effect, but also in benefits resulting from the combined treatment

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and further surprising beneficial effects compared to a monotherapy applying only one of the pharmaceutically active compounds used in the combinations disclosed herein.

In particular, all the more surprising is the experimental finding that the combination of the present invention results in a beneficial, especially a synergistic, therapeutic effect but also in benefits resulting from combined treatment such as a surprising prolongation of efficacy, a broader variety of therapeutic treatment and surprising beneficial effects on diseases and conditions as specified hereinbefore or hereinafter.

Further benefits when applying the composition of the present invention are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side effects. This is in accordance with the desires and requirements of the patients to be treated.

The results of the studies clearly show that the composition according to the present invention can be used for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of

- (a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
- (b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension; and
- (c) endothelial dysfunction with or without hypertension.

The compositions of the present invention can also be used for the prevention and delay of progression and preferably the treatment of other diseases.

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A preferred composition comprises the combination of the (+)-enantiomer of the hydrochloride of fadrozole and valsartan or valsartan combined with hydrochlorothiazide.

Preferably, the jointly therapeutically effective amounts of an AT<sub>1</sub>-receptor antagonist or of an AT<sub>1</sub>-receptor antagonist combined with a diuretic, in each case, in free or pharmaceutically acceptable salt form and an aldosterone synthase inhibitor in free or pharmaceutically acceptable salt form can be administered simultaneously or sequentially in any order, separately or in a fixed combination.

Furthermore, the invention relates to a method of the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of

- (a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
  - (b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension; and
  - (c) endothelial dysfunction with or without hypertension;
- comprising administering to a warm-blooded animal, including man, a therapeutically effective amount of an aldosterone synthase inhibitor in free or pharmaceutically acceptable salt form either alone or in combination with an AT<sub>1</sub>-receptor antagonist or in combination with an AT<sub>1</sub>-receptor antagonist combined with a diuretic, in each case, in free or pharmaceutically acceptable salt form.

Furthermore, the invention relates to the use of a

- (a) pharmaceutical composition comprising
  - (i) an AT<sub>1</sub>-receptor antagonist or an AT<sub>1</sub>-receptor antagonist combined with a diuretic, or, in each case, a pharmaceutically acceptable salt thereof,
  - (ii) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof and
  - (iii) a pharmaceutically acceptable carrier; or
- (b) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,

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for the manufacture of a medicament for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of

(α) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;

(β) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension; and

(γ) endothelial dysfunction with or without hypertension.

The present invention likewise relates to a "kit-of-parts", for example, in the sense that the components to be combined according to the present invention can be dosed independently or by use of different fixed combinations with distinguished amounts of the components, i.e. simultaneously or at different time points. The parts of the kit of parts can then e.g. be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Preferably, the time intervals are chosen such that the effect on the treated disease or condition in the combined use of the parts is larger than the effect that would be obtained by use of only any one of the components.

The invention furthermore relates to a commercial package comprising the combination according to the present invention together with instructions for simultaneous, separate or sequential use.

These pharmaceutical preparations are for enteral, such as oral, and also rectal or parenteral, administration to homeotherms, with the preparations comprising the pharmacological active compound either alone or together with customary pharmaceutical auxiliary substances. For example, the pharmaceutical preparations consist of from about 0.1 % to 90 %, preferably of from about 1 % to about 80 %, of the active compound. Pharmaceutical preparations for enteral or parenteral, and also for ocular, administration

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are, for example, in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner which is known per se, for example using conventional mixing, granulation, coating, solubilizing or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compound with solid excipients, if desired granulating a mixture which has been obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

Preferred dosages for the active ingredients of the pharmaceutical combination according to the present invention are therapeutically effective dosages, especially those which are commercially available.

Normally, in the case of oral administration, an approximate daily dose of from about 1 mg to about 360 mg is to be estimated e.g. for a patient of approximately 75 kg in weight.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

Valsartan, as a representative of the class of AT<sub>1</sub>-receptor antagonists, will be supplied in the form of suitable dosage unit form, for example, a capsule or tablet, and comprising a therapeutically effective amount, e.g. from about 20 to about 320 mg, of valsartan which may be applied to patients. The application of the active ingredient may occur up to three times a day, starting e.g. with a daily dose of 20 mg or 40 mg of valsartan, increasing via 80 mg daily and further to 160 mg daily up to 320 mg daily. Preferably, valsartan is applied twice a day with a dose of 80 mg or 160 mg, respectively, each. Corresponding doses may be taken, for example, in the morning, at mid-day or in the evening.

The following examples illustrate the above-described invention; however, it is not intended to restrict the scope of this invention in any manner.

Formulation Example 1:

## Film-Coated Tablets:

Components	Composition Per Unit (mg)	Standards
Granulation		
Valsartan [= active ingredient]	80.00	
Microcrystalline cellulose/ Avicel PH 102	54.00	NF, Ph. Eur
Crospovidone	20.00	NF, Ph. Eur
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	0.75	Ph. Eur/ NF
Magnesium stearate	2.5	NF, Ph. Eur
Blending		
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	0.75	Ph. Eur/ NF
Magnesium stearate	2.00	NF, Ph. Eur
Coating		
Purified water <sup>1</sup>	-	
DIOLACK pale red 00F34899	7.00	
Total tablet mass	167.00	

<sup>1</sup> Removed during processing.

The film-coated tablet is manufactured e.g. as follows:

A mixture of valsartan, microcrystalline cellulose, crospovidone, part of the colloidal anhydrous silica/colloidal silicon dioxide/Aerosile 200, silicon dioxide and magnesium stearate is premixed in a diffusion mixer and then sieve through a screening mill. The resulting mixture is again pre-mixed in a diffusion mixer, compacted in a roller compacter and then sieve through a screening mill. To the resulting mixture, the rest of the colloidal anhydrous silica/colloidal silicon dioxide/Aerosile 200 are added and the final blend is made in a diffusion mixer. The whole mixture is compressed in a rotary tabletting machine and the tablets are coated with a film by using Diolack pale red in a perforated pan.

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**Formulation Example 2:**

Film-coated tablets:

Components	Composition Per Unit (mg)	Standards
Granulation		
Valsartan [= active ingredient]	160.00	
Microcrystalline cellulose/ Avicel PH 102	108.00	NF, Ph. Eur
Crospovidone	40.00	NF, Ph. Eur
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	1.50	Ph. Eur/ NF
Magnesium stearate	5.00	NF, Ph. Eur
Blending		
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	1.50	Ph. Eur/ NF
Magnesium stearate	4.00	NF, Ph. Eur
Coating		
Opadry Light Brown 00F33172	10.00	
Total tablet mass	330.00	

The film-coated tablet is manufactured e.g. as described in Formulation Example 1.

**Formulation Example 3:****Film-Coated Tablets:**

Components	Composition Per Unit (mg)	Standards
<b>Core: Internal phase</b>		
Valsartan [= active ingredient]	40.00	
Silica, colloidal anhydrous (Colloidal silicon dioxide) [= Glidant]	1.00	Ph. Eur, USP/NF
Magnesium stearate [= Lubricant]	2.00	USP/NF
Crospovidone [Disintegrant]	20.00	Ph. Eur
Microcrystalline cellulose [= Binding agent]	124.00	USP/NF
<b>External phase</b>		
Silica, colloidal anhydrous, (Colloidal silicon dioxide) [= Glidant]	1.00	Ph. Eur, USP/NF
Magnesium stearate [Lubricant]	2.00	USP/NF
<b>Film coating</b>		
Opadry® brown OOF 16711 <sup>1)</sup>	9.40	
Purified Water <sup>2)</sup>	-	
<b>Total tablet mass</b>	199.41	

<sup>1)</sup> The composition of the Opadry® brown OOF16711 coloring agent is tabulated below.

<sup>2)</sup> Removed during processing

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**Opadry® Composition:**

Ingredient	Approximate % Composition
Iron oxide, black (C.I. No. 77499, E 172)	0.50
Iron oxide, brown (C.I. No. 77499, E 172)	0.50
Iron oxide, red (C.I. No. 77491, E 172)	0.50
Iron oxide, yellow (C.I. No. 77492, E 172)	0.50
Macrogol (Ph. Eur)	4.00
Titanium dioxide (C.I. No. 77891, E 171)	14.00
Hypromellose (Ph. Eur)	80.00

The film-coated tablet is manufactured e.g. as described in Formulation Example 1.

**Formulation Example 4:**

**Capsules:**

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	80.00
Microcrystalline cellulose	25.10
Crospovidone	13.00
Povidone	12.50
Magnesium stearate	1.30
Sodium lauryl sulphate	0.60
Shell	
Iron oxide, red (C.I. No. 77491, EC No. E 172)	0.123
Iron oxide, yellow (C.I. No. 77492, EC No. E 172)	0.123
Iron oxide, black (C.I. No. 77499, EC No. E 172)	0.245
Titanium dioxide	1.540
Gelatin	74.969
Total tablet mass	209.50

The tablet is manufactured e.g. as follows:

**Granulation/Drying**

Valsartan and microcrystallin cellulose are spray-granulated in a fluidised bed granulator with a granulating solution consisting of povidone and sodium lauryl sulphate dissolved in purified water. The granulate obtained is dried in a fluidised bed dryer.

**Milling/Blending**

The dried granulate is milled together with crospovidone and magnesium stearate. The mass is then blended in a conical screw type mixer for approximately 10 minutes.

**Encapsulation**

The empty hard gelatin capsules are filled with the blended bulk granules under controlled temperature and humidity conditions. The filled capsules are dedusted, visually inspected, weightchecked and quarantined until by Quality assurance department.

**Formulation Example 5:****Capsules:**

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	160.00
Microcrystalline cellulose	50.20
Crospovidone	26.00
Povidone	25.00
Magnesium stearate	2.60
Sodium lauryl sulphate	1.20
Shell	
Iron oxide, red (C.I. No. 77491, EC No. E 172)	0.123
Iron oxide, yellow (C.I. No. 77492, EC No. E 172)	0.123
Iron oxide, black (C.I. No. 77499, EC No. E 172)	0.245
Titanium dioxide	1.540
Gelatin	74.969
Total tablet mass	322.00

The formulation is manufactured e.g. as described in Formulation Example 4.

**Formulation Example 6:****Hard Gelatine Capsule:**

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	80.00
Sodium laurylsulphate	0.60
Magnesium stearate	1.30
Povidone	12.50
Crospovidone	13.00
Microcrystalline cellulose	21.10
Total tablet mass	130.00

**Formulation Example 7:**

A hard gelatin capsule, comprising as active ingredient e.g. (S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'(1H-tetrazol-5-yl)biphenyl-4-yl-methyl]amine, can be formulated, for example, as follows:

**Composition:**

(1) valsartan	80.0 mg
(2) microcrystalline cellulose	110.0 mg
(3) polyvidone K30	45.2 mg
(4) sodium lauryl sulfate	1.2 mg
(5) crospovidone	26.0 mg
(6) magnesium stearate	2.6 mg

Components (1) and (2) are granulated with a solution of components (3) and (4) in water. The components (5) and (6) are added to the dry granulate and the mixture is filled into size 1 hard gelatin capsules.

- 20 -

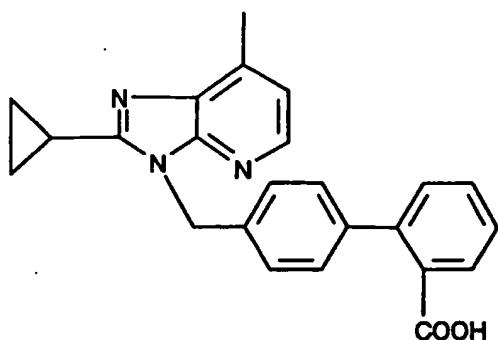
**Formulation Example 8:**

Component	Amount per Unit (mg)
<b>Core</b>	
fadrozole (hydrochloride), Hemihydrate	1.035 <sup>1)</sup>
Aerosil 200 (Silica aerogel)	0.200
Avicel PH 102 (Cellulose)	37.300
Cellulose-HP-M 603 (Hydroxypropyl methylcellulose)	2.000
Lactose ground	53.965
Magnesium stearate	0.500
Polyvinyl-polypyrrolidone XL	5.000
Weight of Core	100.000
<b>Coating</b>	
Cellulose-HP-M 603 (Hydroxypropyl methylcellulose)	1.837
Iron oxide, red, 17266I	0.017mg
ron oxide, yellow, 17268	0.017 mg
Polyethylene glycol 8000, in flakes	0.333 mg
Talc, PH	1.330 mg
Titanium dioxide	0.466
Weight of Coating	4.000

<sup>1)</sup> 1.035 mg CGS 16 949 A hemihydrate is equivalent to 1.000 mg anhydrate.

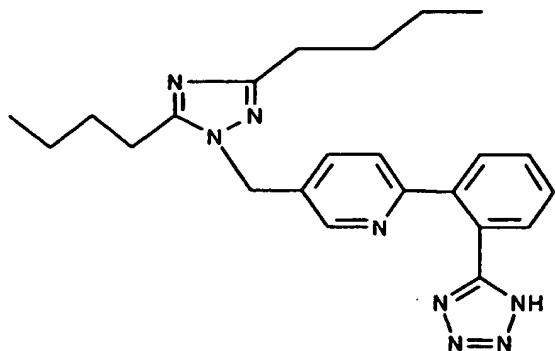
What is claimed is

1. Use of a pharmaceutical composition comprising
  - (i) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof alone or in combination with,
  - (ii) an AT<sub>1</sub>-receptor antagonist or an AT<sub>2</sub> receptor antagonist combined with a diuretic or, in each case, a pharmaceutically acceptable salt thereof and
  - (iii) a pharmaceutically acceptable carrier;for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of
  - (a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
  - (b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension; and
  - (c) endothelial dysfunction with or without hypertension.
2. Use according to claim 1 wherein said AT<sub>1</sub>-receptor antagonist is selected from the group consisting of valsartan, losartan, candesartan, eprosartan, irbesartan, saprisartan, tasosartan, telmisartan, the compound with the designation E-1477 of the following formula

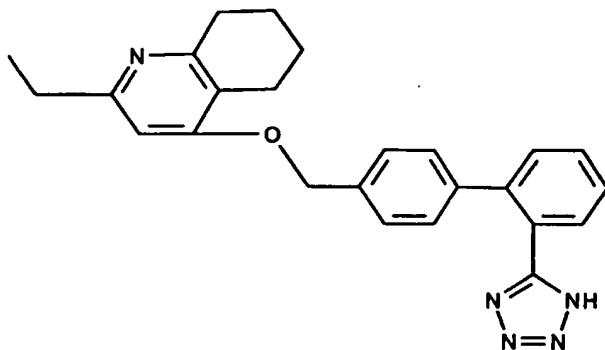


- 22 -

the compound with the designation SC-52458 of the following formula

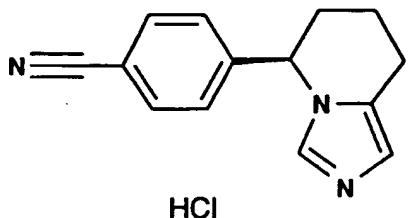


and the compound with the designation ZD-8731 of the following formula



or, in each case, a pharmaceutically acceptable salt thereof.

3. Use according to claim 2 wherein said AT<sub>1</sub>-receptor antagonist is valsartan or a pharmaceutically acceptable salt thereof.
4. Use according to any one of claims 1 to 3 wherein said aldosterone synthase inhibitor is selected from the group consisting of anastrozole, fadrozole (including the (+)-enantiomer thereof, and exemestane, or, in each case where applicable, a pharmaceutically acceptable salt thereof.
5. Use according to any one of claims 1 to 4 wherein said aldosterone synthase inhibitor is (+)-enantiomer of the hydrochloride of fadrozole of formula



6. Use according to any one of claims 1 to 5 wherein the diuretic is hydrochlorothiazide.

7. Use of a pharmaceutical composition comprising  
an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,  
for the manufacture of a medicament for the prevention of, delay of progression of,  
treatment of a disease or condition selected from the group consisting of  
(a) hypertension, congestive heart failure, renal failure, especially chronic renal failure,  
restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery  
bypass surgery;  
(b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity,  
nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post  
myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial  
dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling  
following hypertension (antiproliferative effect of the combination), all these diseases or  
conditions associated with or without hypertension; and  
(x) endothelial dysfunction with or without hypertension.

8. A pharmaceutical composition comprising:

(i) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof either  
alone or in combination with,  
(ii) an AT<sub>1</sub>-receptor antagonist or an AT<sub>1</sub> receptor antagonist combined with a diuretic or,  
in each case, a pharmaceutically acceptable salt thereof; and  
(iii) a pharmaceutically acceptable carrier;  
for the prevention of, delay of progression of, treatment of a disease or condition selected  
from the group consisting of

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- (a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
- (b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension; and
- (c) endothelial dysfunction with or without hypertension.

9. A method for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of

- (a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
  - (b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension; and
  - (c) endothelial dysfunction with or without hypertension;
- comprising administering to a warm-blooded animal, including man, a therapeutically effective amount of an aldosterone synthase inhibitor in free or pharmaceutically acceptable salt form.

10. Method according to claim 9 further comprising administering a therapeutically effective amount of an AT<sub>1</sub>-receptor antagonist or an AT<sub>1</sub> receptor antagonist combined with a diuretic, in each case, in free or pharmaceutically acceptable salt form.

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60/196,742 12 April 2000 (12.04.2000) US
- (71) Applicant (*for all designated States except AT, US*): **NOVARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).**
- (71) Applicant (*for AT only*): **NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H. [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).**
- (72) Inventor; and
- (75) Inventor/Applicant (*for US only*): **STEELE, Ronald, Edward [US/US]; 101 Naughtright Road, Long Valley, NJ 07853 (US).**
- (74) Agent: **BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).**
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**Published:**

- *with international search report*
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**WO 01/76574 A3**

(54) Title: **NOVEL MEDICAL USE OF ALDOSTERONE SYNTHASE INHIBITORS ALONE OR IN COMBINATION WITH AT1-RECEPTOR ANTAGONISTS**

(57) Abstract: The invention relates to a pharmaceutical composition, of (i) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof either alone or in combination with (ii) an AT<sub>1</sub>-receptor antagonist combined with a diuretic, or in each case, a pharmaceutically acceptable salt thereof and (iii) a pharmaceutically acceptable carrier.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/04116

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/00 A61K31/4196 A61K31/437 A61K31/5685 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, MEDLINE, EMBASE, SCISEARCH, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S.BUDAVARI EDITOR: "The Merck Index, 12th Edition", MERCK & CO., INC., WHITEHOUSE STATION, N.J., U.S.A. XP002178362 page 105, paragraph 667 page 666, paragraph 3969 ---	1,4,5,8, 9
X	US 5 252 565 A (PEET NORTON P ET AL) 12 October 1993 (1993-10-12) column 1, line 10-49 column 3, line 30-36 ---	1,7-9
X	US 5 906 987 A (CHWALISZ KRISTOF ET AL) 25 May 1999 (1999-05-25) column 3, line 22-45 column 9, line 14-32 examples 4,5 claims 1,20 ---	1,7-9
	-/-	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

12 February 2002

Date of mailing of the international search report

25.02.2002

Name and mailing address of the ISA

European Patent Office, P.O. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
Fax (+31-70) 340-3016

Authorized officer

Bazzanini, R

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 01/04116

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Description of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 03180 A (FERGUSON MARK WILLIAM JAMES ;UNIV MANCHESTER (GB); ASHCROFT GILLIA) 29 January 1998 (1998-01-29) claims 1,14,18,21 ---	1
X	US 5 972 921 A (HALONEN KAIJA ET AL) 26 October 1999 (1999-10-26) claims 1,2,8 ---	1,4,5, 7-9
X	PATENT ABSTRACTS OF JAPAN vol. 1997, no. 07, 31 July 1997 (1997-07-31) & JP 09 071586 A (YAMANOUCHI PHARMACEUT CO LTD), 18 March 1997 (1997-03-18) abstract ---	1,7-9
A	MASATO H ET AL: "ALGAAS/GAAS/INGAAS DOUBLE-DOPED QUANTUM-WELL HEMTS FOR LOW DISTORTION AMPLIFIER" EXTENDED ABSTRACTS OF THE INTERNATIONAL CONFERENCE ON SOLID STATE DEVICES AND MATERIALS, JAPAN SOCIETY OF APPLIED PHYSICS, TOKYO, JA, 29 August 1993 (1993-08-29), pages 715-717, XP000409466 page 703, left-hand column, paragraph 3 -page 704, column 3, paragraph 1 table IX ---	4,5
A	WO 00 02543 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); GASPARO MARC DE (C) 20 January 2000 (2000-01-20) claims 1,5 ---	1-10
A	FR 2 766 821 A (SANOFI SA) 5 February 1999 (1999-02-05) page 2, line 21-33 ---	1-10
A	WO 99 45779 A (SMITHKLINE BEECHAM CORP ;VENKATESH GOPADI M (US)) 16 September 1999 (1999-09-16) claims 1,2,10-18 ---	1-10
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/04116

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HAGMANN M ET AL: "SC-52458, an orally active angiotensin II-receptor antagonist: Inhibition of blood pressure response to angiotensin II challenges and pharmacokinetics in normal volunteers." JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, vol. 29, no. 4, 1997, pages 444-450, XP001053467 ISSN: 0160-2446 abstract ---	1-10
A	MAXFIELD E K ET AL: "Angiotensin II receptor blockade improves nerve function, modulates nerve blood flow and stimulates endoneurial angiogenesis in streptozotocin-diabetic rats." DIABETOLOGIA, vol. 36, no. 12, 1993, pages 1230-1237, XP001053448 ISSN: 0012-186X abstract page 1235, right-hand column, paragraph 2 ---	1-10
P,A	VIIGIMAA M ET AL: "Tasosartan and hydrochlorothiazide as combination therapy in the treatment of severe essential hypertension: Comparison with enalapril." CARDIOVASCULAR DRUGS AND THERAPY, vol. 14, no. 4, August 2000 (2000-08), pages 447-449, XP001053452 ISSN: 0920-3206 page 447, left-hand column, paragraph 1 page 448, right-hand column, paragraph 2 -----	1-10

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 01/04116

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  

Although claims 1-6 9-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  

see FURTHER INFORMATION sheet PCT/ISA/210
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-10

4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

Claims searched incompletely: 1-10.

Present claims 1-10 relate to compounds defined by reference to a desirable characteristic or property, namely an active compound capable of inhibiting the aldosterone synthase (also reported to have an aromatase inhibitory effect), an AT1-receptor antagonist, and a diuretic.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned in claims 2-6.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1, 4, 5, 7-9 (all partially)

Use of an aldosterone synthase inhibitor for the manufacture of a medicament for the prevention of, delay of progression of, treatment of hypertension including hypertension in the elderly, familial dyslipidemic hypertension and remodeling following hypertension.

2. Claims: 1, 4, 5, 7-9 (all partially)

Use of an aldosterone synthase inhibitor for the manufacture of a medicament for the prevention of, delay of progression of, treatment of congestive heart failure, survival post myocardial infarction (MI), coronary heart diseases, all these diseases associated with or without hypertension, as far as not comprised in invention 1.

3. Claims: 1, 4, 5, 7-9 (all partially)

Use of an aldosterone synthase inhibitor for the manufacture of a medicament for the prevention of, delay of progression of, treatment of renal failure and nephropathy, all these diseases associated with or without hypertension as far as not comprised in invention 1.

4. Claims: 1, 4, 5, 7-9 (all partially)

Use of an aldosterone synthase inhibitor for the manufacture of a medicament for the prevention of, delay of progression of, treatment of restenosis after percutaneous transluminal angioplasty and restenosis after coronary artery bypass surgery, all these diseases associated with or without hypertension as far as not comprised in invention 1.

5. Claims: 1, 4, 5, 7-9 (all partially)

Use of an aldosterone synthase inhibitor for the manufacture of a medicament for the prevention of, delay of progression of, treatment of atherosclerosis associated with or without hypertension as far as not comprised in invention 1.

6. Claims: 1, 4, 5, 7-9 (all partially)

Use of an aldosterone synthase inhibitor for the manufacture of a medicament for the prevention of, delay of progression of, treatment of insulin resistance, diabetes mellitus type 2 and syndrome X, all these diseases associated with or

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

without hypertension as far as not comprised in invention 1.

7. Claims: 1, 4, 5, 7-9 (all partially)

Use of an aldosterone synthase inhibitor for the manufacture of a medicament for the prevention of, delay of progression of, treatment of obesity associated with or without hypertension as far as not comprised in invention 1.

8. Claims: 1, 4, 5, 7-9 (all partially)

Use of an aldosterone synthase inhibitor for the manufacture of a medicament for the prevention of, delay of progression of, treatment of hypothyroidism associated with or without hypertension as far as not comprised in invention 1.

9. Claims: 1, 4, 5, 7-9 (all partially)

Use of an aldosterone synthase inhibitor for the manufacture of a medicament for the prevention of, delay of progression of, treatment of increase of formation of collagen and fibrosis, all these diseases associated with or without hypertension as far as not comprised in invention 1.

10. Claims: 1, 4, 5, 7-9 (all partially)

Use of an aldosterone synthase inhibitor for the manufacture of a medicament for the prevention of, delay of progression of, treatment of endothelial dysfunction associated with or without hypertension as far as not comprised in invention 1.

11. Claims: 1 (partially), 2-3 (completely), 4-5 (partially), 6 (completely), 7-9 (partially), 10 (completely)

Use of an aldosterone synthase inhibitor in combination with an AT1-receptor antagonist or an AT2-receptor antagonist combined with a diuretic for the manufacture of a medicament for the prevention of, delay of progression of, treatment of hypertension including hypertension in the elderly, familial dyslipidemic hypertension, remodeling following hypertension and also congestive heart failure, survival post myocardial infarction (MI), coronary heart diseases, renal failure, nephropathy, restenosis after percutaneous transluminal angioplasty, restenosis after coronary artery bypass surgery, atherosclerosis, insulin resistance, syndrome X, diabetes mellitus type 2, obesity, hypothyroidism, increase of formation of collagen, fibrosis, and endothelial dysfunction, all these diseases associated with or without hypertension.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/04116

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
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